SYNTHETIC STUDIES OF HALICHONDRIN B, AN ANTITUMOR POLYETHER MACROLIDE ISOLATED FROM A MARINE SPONGE 5. A HIGHLY CONCISE AND EFFICIENT SYNTHESIS OF THE C37~C54 TRICYCLIC JKL-RING PART

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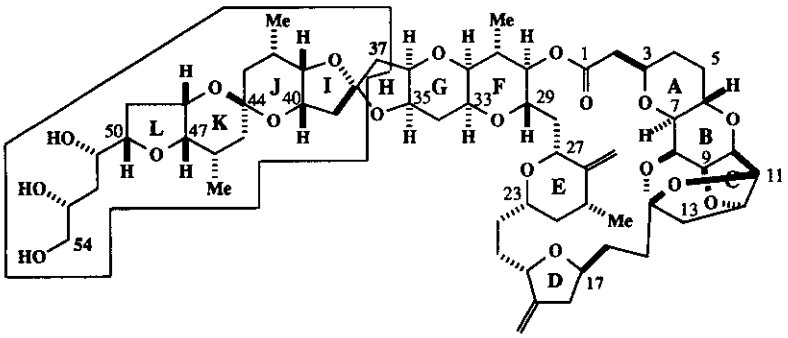
Abstract - A concise and efficient synthesis of C37~C54 tricyclic JKL-ring unit (**2**) of halichondrin B (**1**) utilizing C_2-symmetric spiroketal derivative (**5**) as a synthetic key intermediate, easily provided from dimethyl L-(+)-tartrate, is reported.

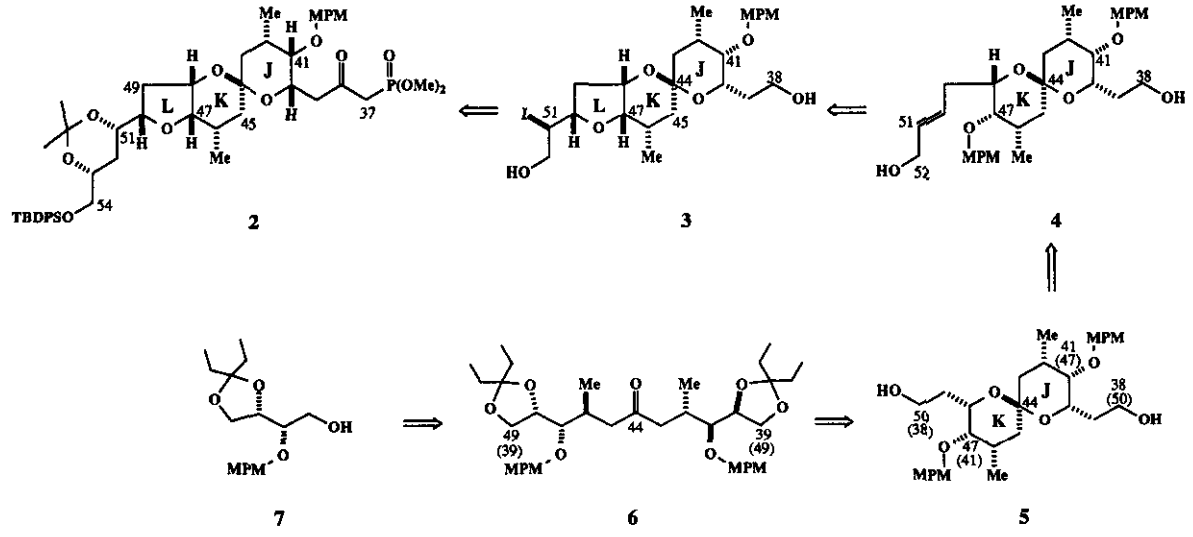
Halichondrin B (**1**) is a representative compound of the antitumor polyether macrolides in the halichondrin family, isolated from a marine sponge *Halichondria okadai* Kadota by Uemura, Hirata and co-workers in 1985.[1] Synthetic challenges toward a total synthesis of halichondrins by synthetic organic chemists[2] have been reported due to the highly complex chemical structure as well as important biological activities, the first total synthesis of halichondrin B (**1**) and norhalichondrin B was achieved by Kishi and co-workers in 1992.[2f] In connection with our synthetic program of **1**, we reported the stereoselective syntheses of four convenient synthetic subunits.[3] In this paper, we describe a highly efficient, concise and stereoselective synthesis of the C37~C54 tricyclic (JKL-rings) unit (**2**) from dimethyl L-(+)-tartrate.



Halichondrin B (1)

This paper is dedicated to the memory of Professor Yoshio Ban.

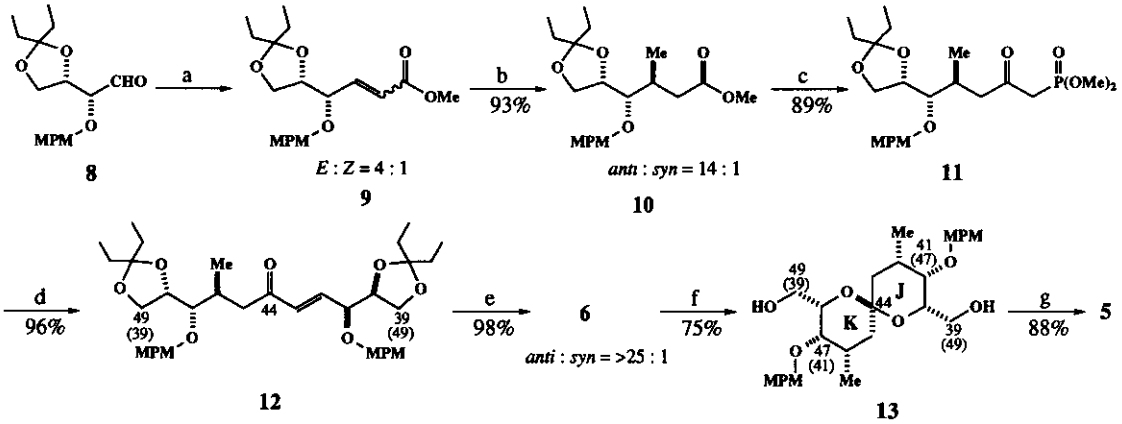
Our synthetic analysis is summarized in Scheme 1. The most significant point to this analysis is utilizing the C_2-symmetric spirocyclic diol (**5**),[4] easily derived from dimethyl L-(+)-tartrate *via* the C_2-symmetric ketone (**6**), as a synthetic key compound. Furthermore, the tricyclic iodohydrin (**3**), which has a suitable configuration for the introduction of the C_{51} oxygenated asymmetric center by epoxidation, could be expected to be efficiently and stereoselectively prepared from the allyl alcohol (**4**) by an iodoetherification reaction after conversion of **5** to **4** *via* a monoprotection step of the two hydroxyl groups.



Scheme 1

The key spirocyclic diol (**5**) was concisely prepared from the known alcohol (**7**),[5] derived from dimethyl L-(+)-tartrate, by using two stereocontrolled conjugate additions of Me_2CuLi to γ-alkoxy-α,β-unsaturated carbonyl compounds[6] in order to introduce two methyl groups at the C_{42} and C_{46} positions,[7] as shown in Scheme 2. The first conjugate addition to the γ-(4-methoxy)phenylmethoxy-α,β-unsaturated ester (**9**), converted from **7** *via* two steps, proceeded successfully and stereoselectively to afford the desired adduct (**10**) with 3,4-*anti* stereochemistry[8] in a 14 : 1 ratio according to Hannessian's procedure.[6g] A more electrophilic γ-(*p*-methoxy)benzyloxy-α,β-unsaturated ketone (**12**) was prepared by Horner-Emmons coupling reaction of the aldehyde (**8**) and the β-ketophosphonate (**11**), obtained by treatment of the ester (**10**) with $LiCH_2P(O)(OMe)_2$ in THF at -78 °C.[9] The second conjugate addition of Me_2CuLi to **12** without Me_3SiCl also proceeded cleanly and stereoselectively to give the desired ketone (**6**) with a high selectivity of more than 25 : 1 in 98% yield. When **6** was exposed to 6N H_2SO_4 in THF at room temperature, removal of the pentylidene groups and subsequent spiroketalization gradually proceeded to produce a pure C_2-symmetrical spiroketal derivative (**13**) as a single diastereomer. One carbon homologation of **13** *via* Swern oxidation[10] and Wittig reaction with

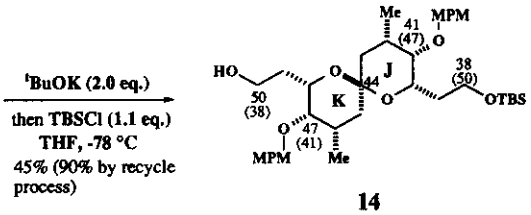
$Ph_3P{=}CH_2$ followed by hydroboration with $(Sia)_2BH$ afforded **5**.[11]



a) $(EtO)_2P(O)CH_2CO_2Me$, ^nBuLi, THF, -78°C. b) Me_2CuLi, TMSCl, THF-Et_2O (4 : 1), -20°C. c) $(MeO)_2P(O)Me$, ^nBuLi, THF, -78°C. d) ^nBuLi, THF, -78°C, then addtion of **8**. e) Me_2CuLi, THF-Et_2O (4 . 1), -78~-20°C. f) 6N H_2SO_4-THF (1 . 3), room temperature g) 1) Swern oxid.; 2) $Ph_3P^+MeBr^-$, ^{t}BuOK, THF, -78~0 °C (97% *via* 2 steps); 3) $(Sia)_2BH$, -20°C then H_2O_2, NaOH, THF

Scheme 2

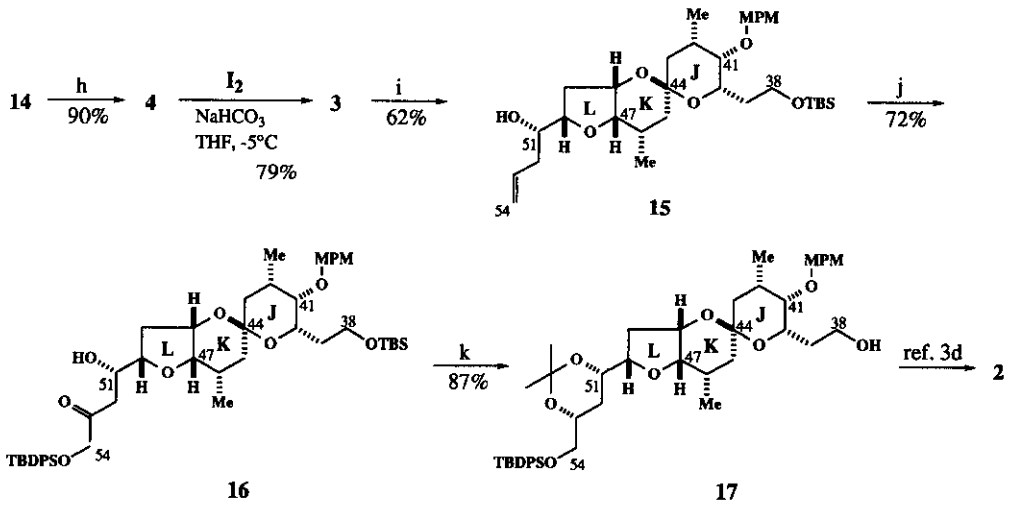
The next step in our synthetic program was to break the C_2-symmetry of **5** by protecting only one of the two primary hydroxyl groups with TBSCl, as shown in Scheme 3. Due to the failure of many efforts[12] to produce **14** effectively, we tried to find a novel reaction condition. When the dipotassium salt of **5**, generated with ^{t}BuOK (2 eq.) in THF at -78 °C, was trapped with TBSCl (1.1 eq.), the desired monoprotected silyl ether (**14**) was obtained in 45% yield with a trace of the disilyl ether. The unreacted starting diol (**5**) was easily recovered by silica gel column chromatography since the polarity of the diol (**5**) and monosilyl ether (**14**) was remarkably different.[13] An effective conversion of **5** to **14** was achieved by repeating this recycling process three times.



Scheme 3

Finally, the synthesis of **17** from **14** was carried out *via* a highly stereoselective construction of the L-ring and the introduction of the two asymmetric centers at the C_{51} and C_{53} positions as shown in Scheme 4. When the allyl alcohol (**4**) , converted from **14** *via* three coventional steps, was treated with iodine in THF at -5 °C in the presence of $NaHCO_3$, an iodoetherification reaction stereoselectively and smoothly occurred to give the desired tricyclic iodohydrin (**3**) as a single diastereomer. Transformation of **3** to the corresponding epoxide by

treatment with ^{t}BuOK in THF at -20 °C, followed by addition of the vinylmagnessium bromide in the presence of CuI afforded allyl alcohol (**15**), which was led to **17** *via* a stereoselective reduction of the β-hydroxy ketone (**16**) with $NaBH_4$ in the presence of $MeOBEt_2$ in MeOH and THF.[14] Since the conversion of **17** to **2** was already reported[3d], we were able to establish a concise and efficient synthetic route for the C_{37}~C_{54} subunit (**2**) from dimethyl L-(+)-tartrate. Recently, we succeeded in synthesizing the C_1~C_{37} macrolactone and the C_{28}~C_{54} polyether portions by efficiently connecting our four synthetic subunits. These results will be reported soon.



h) 1) Swern oxid.; 2) $(^{i}PrO)_2P(O)CH_2CO_2Et$, ^{t}BuOK, THF, -78°C (91% *via* 2 steps); 3) DIBAH, CH_2Cl_2, -78°C (99%). i) 1) ^{t}BuOK, THF, -20°C (82%); 2) vinylMgBr, CuI, Et_2O (76%); j) 1) TESCl, imidazole, CH_2Cl_2 (95%); 2) OsO_4, NMO, H_2O-acetone (1 : 10) (95%); 3) TBDPSCl, imidazole, CH_2Cl_2, room temperature (95%); 4) Swern oxid. (91%); 5) 1N HCl-THF (1 : 4) (91%). k) 1) Et_2BOMe, $NaBH_4$, MeOH-THF (1 . 2); 2) CSA, $Me_2C(OMe)_2$, benzene (87% *via* 2 steps)

Scheme 4

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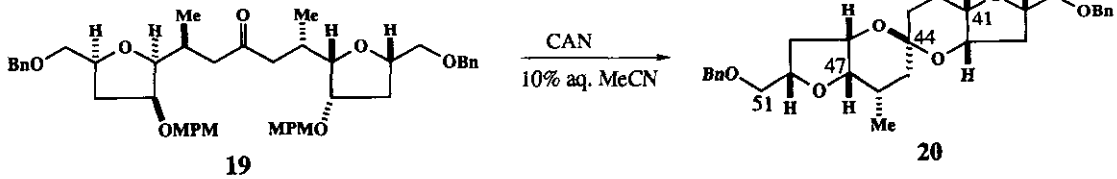
4 Salomon and co-workers have independently synthesized C_2-symmetrical spirotetracyclic compound (**20**) from ketone (**19**), derived from D-mannitol by using two conjugate addition reactions of $Me_2Cu(CN)Li_2$ in the presence of TMSCl in THF at -75 °C to a γ-alkoky-α,β-unsaturated acylsilane and a ketone, as a model compound correcponding to the C_{37}~C_{51} portion of halichondrin B (**1**).[2J]



19 **20**

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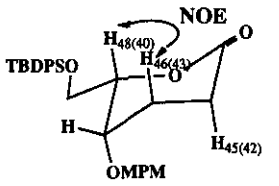
7652.

7 Unless otherwise noted, numbering is based on those of halichondrin B (**1**).

8 The stereochemistry of methyl ester (**10**) was assigned on the basis of the ^{1}H-nmr data (*J*-value between $H_{45(43)}$ axial proton and $H_{46(42)}$ proton, and ^{1}H-NOESY) after conversion of **10** to the six membered lactone (**18**) *via* the conventional 3 steps, as shown below.

10 —(1) 2N HCl-MeOH (1 : 1); (2) TBDPSCl, imidazole; (3) TosOH, MeOH, 57%→ 

$J_{45(42)}$-$J_{46(43)}$= 9.0 Hz

18

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11 **5**: $[\alpha]_D^{23}$ -90° (c= 0.68, $CHCl_3$); ^{1}H-nmr (500 MHz, $CDCl_3$) δ 0.94 (6H, d, J=7.0 Hz), 1.52~1.42 (2H, m), 1.50 (2H, dd, J=4.0, 13.0 Hz), 1.59 (2H, t, J=13.0 Hz), 2.18 (2H, dddd, J=2.0, 4.5, 10.0, 11.0 Hz), 2.11~2.20 (2H, m), 2.20~2.34 (2H, m), 3.19 (2H, s), 3.65 (2H, dt, J=11.0, 4.5 Hz), 3.76~3.81 (2H, m), 3.79 (6H, s), 3.82 (2H, dd, J=1.0, 11.0 Hz), 4.51 (2H, d, J=11.5 Hz), 4.55 (2H, d, J= 11.5 Hz), 6.85 (4H, d, J= 8.5 Hz), 7.26 (4H, d, J= 8.5 Hz). ^{13}C-Nmr (500 MHz, $CDCl_3$); δ 18.16, 30.93, 35.24, 37.94, 55.34, 58.83, 68.52, 74.99, 78.60, 96.84, 113.66, 129.86, 130.92, 159.25.

12 For example: (a) A usual silylation using imidazole and TBSCl in CH_2Cl_2 or DMF at a low temperature (even as low as -20 °C) gave predominantly a disilyl ether. (b) When ^{n}BuLi was used as a base instead of ^{t}BuOK, the silylation reaction didn't proceed at all.

13 Rf value: (**5**) 0.01, (**14**) 0.60, disilyl ether of (**5**) 0.95 (AcOEt : ^{n}hexane=1 : 2).

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